IN THE SPECIFICATION

Following the last page of the specification, please replace the originally filed Sequence Listing with the enclosed Substitute Sequence Listing.

Please replace the paragraph on page 5, lines 10-29, with the following:

The present invention relates to adenovirus vectors containing a minimum packaging signal for producing adenovirus virions. Of special importance is the presence of a CG dinucleotide located downstream of a TTTG sequence within each of the packaging elements. Spacing between the consensus segment 5'-TTTG-3' and the 5'-CG-3' segment located downstream is preferably between 1 and 12 nucleotides. Alternatively, it amy be preferred to configure the consensus segments so that these elements appear on the same surface of the DNA helix. Most preferably, the adenovirus vector of the present invention may contain a packaging element consisting of 5'-TTTGN_8CG-3' (SEQ ID NO:1) which represents a minimal sequence necessary for adenovirus packaging. This sequence is preferably present in multiple copies. One type of minimal packaging sequence is an "A repeat", which contains a consensus sequence. Several A repeat sequences are shown in Table 1.

Please replace the paragraph on page 8, lines 1-22, with the following:

FIG. 1 depicts the adenovirus type 5 packaging domain. (A) A schematic representation of the left end of the adenovirus type 5 genome. Nucleotide positions are indicated by numbers. The inverted terminal repeat (ITR) is represented by a gray box. Viral packaging repeats are termed A repeats I to VII (arrows). The E1A transcriptional start site is indicated by an arrow, and enhancer elements I and II are designated E1A enhancer. (B) The packaging repeat consensus motif. Shown is an alignment of A repeats I (SEQ ID NO:3), II (SEQ ID NO:4), V (SEQ ID NO:7) and VI (SEQ ID NO:8). Nucleotides comprising the bipartite consensus motif for A repeats I, II, V and VI are boxed and enlarged. The consensus motif is shown at the bottom (5'-TTTGN$_8$CG-3' (SEQ ID NO:1)). (C) Alignment of A repeats V and VI in different adenovirus subgroups: Ad 5 (subgroup C) (SEQ ID NO:23), Ad 4 (subgroup E) (SEQ ID NO:24), Ad 12 (subgroup A) (SEQ ID NO:25), Ad 3 (subgroup B) (SEQ ID NO:26), Ad 9 (subgroup D) (SEQ ID NO:27). The positions of AV and AVI are shown by horizontal lines above the sequence. Nucleotides identical between all subgroups are indicated by vertical lines.

Please replace the paragraph on page 10, lines 9-23, with the following:

FIG. 7 depicts multimerized oligonucleotides corresponding to A repeats AI (SEQ ID NO:28) and AVI (SEQ ID NO:29) used to construct recombinant viruses. A dimeric oligonucleotide sequence is shown to simplify the schematic diagram. The potential COUP-TF binding sites in the oligonucleotides are indicated by arrows. Perfect or 4-out-of-5 nucleotide matches to the COUP-TF consensus sequence are shown as closed arrowheads; 3-out-of-5 nucleotide matches to the COUP-TF consensus site are shown as open arrowheads. Perfect, or nearly-perfect, COUP-TF binding sites with a 1 base spacing are found in multiple locations in the AVI oligonucleotide repeat, but not in the AI oligonucleotide repeat.

Please replace the paragraph on page 12, lines 6-25 with the following:

Fig. 10 depicts synthetic oligonucleotides that contain different adenovirus packaging repeats designed with specific repressor binding sites that either overlap the packaging A repeats or are placed between packaging A repeats. (A) The sequence of the wild type AV-AVII oligonucleotide (SEQ ID NO:16). A dimeric copy of this oligonucleotide efficiently directed packaging in a recombinant virus (Fig. 2). A repeats V, VI and VII are indicated and the consensus packaging repeats are encircled. (B) The AV-AVII oligonucleotide is modified (SEQ ID NO:30) (underlined nucleotides) to create a high affinity binding site for the adenovirus-induced E2F-E4-6/7 protein complex overlapping A repeats V and VI (binding site indicated by inverted arrows). (C) The AV-AVII oligonucleotide is modified (SEQ ID NO:31) (underlined nucleotides) to create a high affinity binding site for the *E. coli* lac repressor overlapping and adjacent to A repeat V (binding site indicated by inverted arrows).

Please replace the paragraph beginning on page 14, line 27, and ending on page 15, line 22, with the following:

The present invention also relates to the identification of a minimum adenovirus packaging signal. A minimal packaging sequence of 5'-TTTGN_8CG-3' (SEQ ID NO:1) has been identified. Although eight nucleotides are preferred to separate the left portion of the packaging consensus element (i.e., 5'-TTTG-3') from the right portion (i.e., 5'-CG-3'), this spacing may vary 1 to 12 nucleotides. Alternatively, it may be preferred to configure the consensus segments so that the segments appear on the same surface of the DNA helix. the packaging element may be inserted into the left or right end of the adenovirus vector, preferably within 600 nucleotides from either end. More preferably, this minimal sequence is present at the left end of the genome and is present in multiple copies. Another consensus sequence comprises 5'-ATTTGN_8CG-3' (SEQ ID NO:2) and provides a strong packaging signal in adenovirus vectors. Two copies of this minimal packaging sequence are sufficient to ensure packaging. More than two copies enhance virus packaging. However, any number of this sequence can be inserted into the virus to ensure particle production. "Multimerized" as this term is used in the instant application refers to multiple copies of an element (i.e. packaging or repressing). These elements may be present in single units or in multimers, which preferably means 2-36 repeats and more preferably 2-12 units or elements. One form of the minimal packaging element is an "A repeat", which is derived from adenovirus. Representative A repeats are set forth below in Table 1:

Please replace Table 1 on page 15 with the following Table 1:

TABLE 1

AI:	5'-TTTGGGCGTAACCG-3' (SEQ ID NO:3)
AII:	5'-TTTGGCCATTTTCG-3' (SEQ ID NO:4)
AIII:	5'-TCTGAATAATTTTG-3' (SEQ ID NO:5)
AIV:	5'-TTTGTGTTACTCAT-3' (SEQ ID NO:6)
AV:	5'-TTTGTCTAGGGCCG-3' (SEQ ID NO:7)
AVI:	5'-TTTGACCGTTTACG-3' (SEQ ID NO:8)
AVII:	5'-TTTACGTGGAGACT-3' (SEQ ID NO:9)

Please replace the paragraph on page 19, lines 13-17, with the following:

Another important aspect of the present invention relates to gene therapy vectors that use adenovirus minimal packaging sequence, 5'-TTTGN_8CG-3' (SEQ ID NO:1). (See Provisional patent application no. 60/081,867, incorporated herein by reference).

Please replace the paragraph that begins on page 23, line 29, and ends on page 24, line 16, with the following:

Cellular P-complex is a bona-fide adenovirus packaging component. This complex appears to contain a TATA binding protein (TBP) and a second protein called TAF172 (Timmers et al. 1992, Taggart et al. 1992). P-complex binding is inhibited by ATP and magnesium. Complex formation is observed on all minimal packaging domains that exhibit functional activity *in vivo*. The affinity of the P complex for the different multimeric A repeats *in vitro* correlates well with the ability of the respective cis-acting sequences to support viral DNA packaging *in vivo*. Specifically, AI and AV-VII constitute strong P complex binding sites and they confer maximal packaging activity *in vivo*. The most preferred P-complex binding sites comprise a hexamer of AI and a dimer of AV, AVI and AVII. On the other hand, AVI is noted as a weak binding site for P complex *in vitro*, and it serves as a particularly weak packaging domain *in vivo*. As discussed above, the Ad packaging consensus motif is a bipartite sequence with a conserved AT-rich and a GC-rich half site (5'-TTTGN$_8$CG-3' (SEQ ID NO:1)) (Schmid, et al. (1997)).

Please replace the paragraph on page 27, lines 3-34, with the following:

Virus constructions. Ad5 d1309, the parent for all the viruses described in this report, is a phenotypically wild type virus that contains a unique XbaI cleavage site at 3.8 map units (Jones, et al. (1979)). Plasmid pE1A-194/814 contains the left end Ad5 XbaI fragment (nt 1-1339) with a deletion between nt 194 and 814 and a unique XhoI restriction site at the junction of the deletion. A head-to-tail hexamer of an oligonucleotide containing A repeat VI (5'-TCGACCGCGGGGACTTTGACC-3' (SEQ ID NO:10):5'-TCGAGGTCAAAGTCCCCGCGG-3' (SEQ ID NO:11)) was cloned into the 194/814 deletion. Similarly, head-to-tail hexamers of oligonucleotides containing A repeat I (5'-TCGAGTTGTAGTAAATTTGGG-3' (SEQ ID NO:12):5'-TCGACCCAAATTTACTACAAC-3' (SEQ ID NO:13)) or A repeat II (5'-TCGACCGAGTAAGATTTGGCC-3' (SEQ ID NO:14):5'-TCGAGGCCAAATCTTACTCGG-3' (SEQ ID NO:15)) were cloned into the pE1A-194/814 background. pBR-194/814 and pBR-53/814 have sequences between nt 194 and 814 and nt 53 and 814 deleted. A monomer and dimer of viral sequences is located between nt 334 and 385 which contain AV, AVI, and AVII was cloned into the 194/814 deletion. A dimer of the nt 334 to 385 fragment as well as 12 head-to-tail copies of an oligonucleotide containing AVI (5'-TCGACCGCGGGGACTTTGACC-3' (SEQ ID NO:10):5'-TCGAGGTCAAAGTCCCCGCGG-3' (SEQ ID NO:11)) were cloned into the 53/814 deletion in either orientation. All mutations were verified by nucleotide sequence analysis.

Please replace the paragraph beginning on page 30, line 16, and ending on page 31, line 3, with the following:

Plasmids, probes and competitor fragments. Head-to-tail hexamers of A repeats I and VI, individually, and a dimer of A repeats V-VII were cloned into pUC9. The sequence of a monomer of A repeat I is: 5'-TCGAGTTGTAGTAAATTTGGG-3' (SEQ ID NO:12): 5'-TCGACCCAAATTTACTACAAC-3' (SEQ ID NO:13), a monomer of A repeat VI is: 5'-TCGACCGCGGGGACTTTGACC-3' (SEQ ID NO:10): 5'-TCGAGGTCAAA GTCCCCGCGG-3' (SEQ ID NO:11), a monomer of AV-AVII is: 5'-TCGACCGCGTAATATTTGTCTAGGGCCGCGGGGACTTTGACCGTTTACGTGGAGACT CC-3' (SEQ ID NO:16): 5'-TCGAGGAGTCTCCACGTAAACGGTCAAAGTCCCCGCGGC CCTAGACAAATATTACGCGG-3' (SEQ ID NO:17). The fragments were liberated from the vector by digestion with EcoRI and HindIII, gel purified and ^{32}P-end-labeled with Klenow DNA polymerase and (α-^{32}P)dATP. For the preparation of ITR 1-13 probe, a monomeric oligonucleotide representing the left end 13 nt flanked by Xho/Sal linkers (5'-TCGACATCATCAATAATC-3' (SEQ ID NO:18): 5'-TCGAGATTATTGATGATG-3' (SEQ ID NO:19)) was end-labeled in the same way using (α-^{32}P)dCTP.

Please replace the paragraph beginning on page 31, line 4, and ending on page 32, line 5, with the following:

For the preparation of competitor fragments containing packaging repeats, monomeric oligonucleotides were multimerized using T4 DNA ligase. Selection for head-to-tail multimers was achieved by subsequent digestion using SalI and XhoI, followed by phenol/chloroform extraction and ethanol precipitation. In addition to multimers prepared from the oligonucleotides representing packaging elements I, VI and V-VII described above, A repeat II (5'-TCGACCGAGTAAGATTTGGCC-3' (SEQ ID NO:14):5'-TCGAGGCCA AATCTTACTCGG-3' (SEQ ID NO:15)) and A repeat V (5'-TCGACCGCGTAATATTTGTCC-3' (SEQ ID NO:20):5'-TCGAGGACAAATATTACGCGG-3' (SEQ ID NO:21)) were used as multimeric competitors. Packaging repeat competitor fragments designated LS have the underlined nucleotides shown above in AI, AII, AV, AVI, AV-VI mutated into the sequence 5'GTGCAG-3' (only the upper strand is indicated). the italicized CG dinucleotide in the AV competitor was replaced by an AT in the competitor fragment designated CG. The competitor oligonucleotide representing ITR sequences 1-13 was used in monomeric form and was identical to the one used for probe preparation. The monomeric ITR 10-22 competitor oligonucleotide contains sequences between Ad nt 10-22 flanked by XhoI/SalI linkers. Quantitation of oligonucleotide competitors was performed spectrophotometrically. The amount of specific competitor DNA added per binding reaction is indicated in the text as -fold molar excess of binding sites present in the competitor relative to binding sites present in the probe. This definition, however, is based on the assumption that one binding site (located between nt 1-13) is present in monomeric ITR fragments and that six binding sites are present in hexameric packaging repeat fragments.

Please replace the paragraph on page 39, lines 8-25, with the following:

COUP-TF interacts with adenovirus packaging elements. Database searches revealed that the AVI probe contains a highly conserved dimeric consensus binding sites for a cellular transcription factor, chicken ovalbumin upstream promoter transcription factor (COUP-TF; Cooney et al. (1992)). COUP-TF binds to the consensus sequence 5'-GGTCA-3' when situated as a direct or inverted repeat, with a preferred spacing of 1 base pair, and represented as perfect or imperfect versions of the consensus binding site. These binding sites overlap A repeat VI (5'-GGACTTTGACC-3' (SEQ ID NO:22); the COUP-TF inverted repeat is underlined, and AVI is in bold), only the upper strand is indicated with the COUP half sites underlined and AVI indicated in bold case. Other A repeats contain similar sequence motifs, albeit with less resemblance to the dimeric COUP consensus.